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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	PAPER NUMBER
1654	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,335	VRIJBLOED ET AL.	
	Examiner	Art Unit	
	ANDREW D. KOSAR	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10-13,16-30 and 33-46* is/are pending in the application.

4a) Of the above claim(s) *36-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10-13,16-30 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 10-13, 16-30, 33-45 and new claim 46 are pending. Applicant's supplemental reply filed July 17, 2009 is acknowledged.

Election/Restrictions

Applicant's election with traverse of Group III in the reply filed on June 16, 2009 is acknowledged. The traversal is on the ground(s) that the claims do have unity of invention, in that D1 does not explicitly teach at least one of the amino acids must be N-alkyl substituted and that the teachings of the art would not lead one to arrive at the instant invention. While Applicant's arguments may be persuasive to the extent that the claims as now presented have unity with respect to the teaching of D1 and the prior art, a lack of unity could have been show under alternate means. Annex B, Part I(f) of the Administrative Instructions under PCT states that, "wherein a single claim defines alternatives (chemical or non-chemical)...the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature."

The alternatives must comply with subsections (i)(A) and one of either (i)(B)(1) or (i)(B)(2), which requires that, "all alternatives have a common property or activity" and "a common structure is present, i.e., a significant structural element is shared by all of the alternatives" (B)(1) or "in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains."(B)(2).

In the instant case, the method requires that the compounds have the same activity/function (treating infections), satisfying requirement (A). However, the claim fails to

satisfy either (B)(1) or (B)(2). The claim recites no common structure beyond the presence of the N-substituted Gly and being a 14 amino acid cyclic peptide, thus failing to meet the requirements of (B)(1). Such structure is not significant and shared by all the alternatives, as there are a plurality of amino acids that can be derived for each of the 12 Z-position residues or the two template residues, Thereby presenting a structure that embraces an infinite number of potential compounds. Further, in looking to subsection (f)(iii), it is stated that 'recognized class of chemical compounds' means that, "there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved." One of skill in the art would not recognize these divergent compounds, or other compounds asserted to have said activity/function, as required, to function in the context of the instantly claimed invention. Thus, the claim fails to meet the requirement of (B)(2), and the holding of lack of unity remains proper. The requirement is still deemed proper and is therefore made FINAL.

Claims 36-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 16, 2009.

Applicant's elected species was found to be free of the prior art. The examiner extended the search to the additional species of claim 17-21 and 23-29, also found to be free of the prior art, and then to embrace the generic claim 1. While cyclic peptides of formula I comprising A5-

11, 79, 82, or 83 with an amino acid of the I or K type, are neither taught nor suggested by the prior art, the claims are rejected for non-art related issues below.

Information Disclosure Statement

The listing of references in the specification (e.g. Page 84) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

Please note, the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claims 1 and 11 are objected to because of the following informalities:

Claim 1, the main independent claim is currently 20+ pages in length, and the clarity of the claim would be improved from reordering/arrangement of the variables.

The claims are directed towards compounds of the formula: 

, where Z is defined 18 pages later than the introduction of the variable in the formula (in the current amendment). Furthermore, the claim defines the amino acids by their 'type', and indicates they may also be Gly, Pro "depending on their position in the chains" (page 19). The definition of the

variables C, D, E, F, H, I and K would benefit from being moved to after the proviso (starting at page 24) where the chains and their components are formally introduced. In making this amendment, Gly and Pro are defined as present only at certain positions and the phrase 'depending on...' would not be necessary. Additionally, the variable R^{74} is indented one level more than the other R variables and R^{86} and R^{87} are missing 'or' between the last two variables.

Claim 11 recites non-standard, atypical amino acids in an abbreviated form. The first occurrence of non-standard abbreviations in the claim should be accompanied by their full name.

Claims 34 and 35 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 33 is a pharmaceutical composition while claims 34 and 35 are drawn to plural compositions. Thus, the claim is broader than the claim from which it depends and is not further limiting.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 10-13, 16-30 and 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 is drawn to "compounds... and pharmaceutically acceptable salts thereof." It is unclear whether applicant is claiming a collection, e.g. an array, of compounds and their salts, or whether Applicant intended to claim "A compound… or a pharmaceutically acceptable salt thereof." This is further confused by the presence of dependent claims to "Compounds

according to claim 1" (e.g. claim 10-13, 16 and 17) and "A compound of formula I according to claim 1" (e.g. claim 18), which supports both positions.

In defining formula (I), Applicant defines the variables in  , however the claim lacks a definition for the variables in  , as the claim provides only a definition for  and  . Furthermore,  is defined as optionally "the enantiomer of one of the groups A1 to A69", however only A5-A11, A79, A82 and A83 remain in the claim, and the R variables related to the remaining A moieties have been cancelled from the claims. Additionally, claim 1 recites throughout that variables "can form", however it is unclear if Applicant is intending to positively recite the limitations as alternatives, e.g. "..or X and Y taken together form…".

Furthermore, claim 1 allows for P4 and P9 and/or P2 and P11 to be a group of Type H. It is unclear whether all 4 together form a type H, or whether the compound can have two Type H compounds.

Claim 10 recites that B is "an enantiomer of the groups A5 (with R^2 being H) or A8", and it is unclear if the parenthetical expression is part of the claim, or merely exemplary, and it is unclear how B can be an enantiomer of the groups (plural) A5 or A8. B can only be one amino acid.

Claim 16 recites that P6 can be A1-A69-CO, however A69 has been cancelled from the claims, and claim 1 only allows for A-CO, not A-A-CO, and thus the claim lacks clear antecedent basis.

Claims 18-29 lack clear antecedent basis as "A compound of claim 1" is unclear as to whether it refers back to formula (I) or a portion of formula (I). Further, dependent claims, e.g. claim 18, should recite "The compound of" rather than "A compound" to refer back with proper antecedent basis.

Claim 30 lacks antecedent basis, in that claim 1 does not allow for enantiomers. Furthermore, it is unclear as to what Applicant is intending as the enantiomer of the compound, in that claim 1 only allows for an optional D-isomer amino acid at two position and the amino acids are structurally defined but have no chirality indicated.

Claims 34 and 35 are drawn to "compositions", and it is unclear whether Applicant is claiming a set of compositions, or whether Applicant intended to claim "A composition".

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10-13, 16, 30 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the

time of filing include: (a) Actual reduction to practice; (b) Disclosure of drawings or structural chemical formulas; (c) Sufficient relevant identifying characteristics such as: (i) Complete structure, (ii) Partial structure, (iii) Physical and/or chemical properties or (iv) Functional characteristics when coupled with a known or disclosed correlation between function and structure; (d) Method of making the claimed invention; (e) Level of skill and knowledge in the art and (f) Predictability in the art. While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

Here, the claims are drawn to an infinite number of peptides of the general formula (I). The specification sets forth peptides within the genus, however they are so closely related in structure, they fail to provide description for the breadth of the genus claimed. Table 1 sets forth the peptides reduced to practice:

Example	Sequ.ID	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Template
1	SEQ ID NO:1	Leu	Arg	Leu	Lys	Lys	(BA)G	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro
2	SEQ ID NO:2	Leu	Arg	Leu	hArg	hArg	(EGU)G	Arg	Trp	hArg	Tyr	Arg	Val	^{D}Pro^{L}Pro
3	SEQ ID NO:3	Leu	Arg	Leu	Lys	Lys	(PrA)G	Arg	Trp	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro
4	SEQ ID NO:4	Leu	Arg	Leu	Lys	Lys	(BA)G	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro
5	SEQ ID NO:5	Leu	Arg	Leu	(BA)G	Lys	(BA)G	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro
6	SEQ ID NO:6	Leu	Arg	Leu	Lys	Lys	(PrA)G	Arg	Bip	Lys	Tyr	Arg	Val	^{D}Pro^{L}Pro
7	SeQ ID NO: 7	Arg	Trp	Leu	Lys	Lys	Arg	(PrA)G	Trp	Lys	Tyr	Tyr	Val	^{D}Pro^{L}Pro
8	SEQ ID NO: 8	Arg	Trp	Leu	Gln	(PrA)G	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro
9	SEQ ID NO: 9	Arg	Trp	Leu	Lys	(PrA)G	Arg	Arg	Trp	Lys	Tyr	Tyr	Val	^{D}Pro^{L}Pro
10	SEQ ID NO: 10	Thr	Trp	Leu	Lys	(PrA)G	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro
11	SEQ ID NO: 11	Arg	Trp	Leu	Gln	Lys	Arg	(PrA)G	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro
12	SEQ ID NO: 12	Thr	Trp	Leu	Lys	(PrA)G	Arg	Arg	Trp	Lys	Tyr	Tyr	Arg	^{D}Pro^{L}Pro

and claim 17 sets forth a subgenus with specifically defined amino acids for the various positions, With the above specific species claimed in claims 18-29.

Beyond these compounds, the specification does not provide complete or partial structures for the peptides contemplated, the claims set forth only a partial structure for A and B and while the compounds are asserted to be antimicrobials, the art recognizes that amino acid

substitution results in unpredictable activity, such that one cannot *a priori* predict the activity of a substitution. This knowledge in the art can be reasonably extrapolated to the instant case, as one cannot determine *a priori* from the closely related compounds above that the plurality of structurally unrelated peptides would function as asserted by the disclosure, particularly since there is no structural core retained by the compounds. From the identified compounds of the disclosure, a clear common core is identified and the specification provides preferred species for the various types of amino acids, however the claims breadth is beyond that which is exemplified; and while peptide synthesis is practiced in the art, the synthesis of the myriad of peptides claimed is beyond that of the artisan, with the expectation that they would function as disclosed.

Here, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks a sufficient variety of species to reflect this variance in the genus, being that the disclosed peptides are structurally related (SEQ ID NOs 1-12) to the extent they do not describe the genus, nor is the breadth of the variable amino acids present in the claims described by the preferred embodiments of the types C-F, I or K. While having written description of the compounds of claims 50-57 and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the

specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claims 1, 10-13, 16, 30 and 33-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making/using compounds of table 1 and claims 17-29, does not reasonably provide enablement for making/using compounds beyond those disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are discussed above, and are drawn generally to compounds of formula I, embracing a plurality of compounds.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

As discused above, the art recognizes that amino acid substitution results in unpredictable results on function. For example, RUDINGER (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (Page 6).

Further, MPEP § 2144.08 states, "The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior domains. James Darnell *et al.*, *Molecular Cell Biology* 51 (2d ed. 1990)."

(5) The relative skill of those in the art, (6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The artisan, while skilled in peptide synthesis, would not be able to synthesize compounds embraced by the claimed, particularly since the specification only provides guidance as to making the peptides described above and it does not provide sufficient guidance with regards to making the myriad of non-standard amino acids embraced, nor does it provide guidance as to how one would know which ones to make and use in the peptides claimed that would function commensurate with what is instantly disclosed and claimed.

Furthermore, given the unpredictability in the art, the specification fails to provide sufficient guidance as to how one would use the compounds as antimicrobials, when the art

recognizes that there is unpredictability with regards to the function obtained by amino acid substitution in peptides.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the unpredictable nature of amino acid substitution on the activity and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Allowable Subject Matter

Claims 17-29 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Furthermore, composition claims limited to those peptides would be allowable, however none are currently present.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANDREW D. KOSAR whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654